



11 Publication number : **0 454 089 B1**

12

EUROPEAN PATENT SPECIFICATION

45 Date of publication of patent specification :
17.08.94 Bulletin 94/33

51 Int. Cl.⁵ : **A61K 31/445, A61K 47/32**

21 Application number : **91106600.9**

22 Date of filing : **24.04.91**

54 **Percutaneously absorbable eperisone or tolperisone preparation.**

30 Priority : **27.04.90 JP 112792/90**

43 Date of publication of application :
30.10.91 Bulletin 91/44

45 Publication of the grant of the patent :
17.08.94 Bulletin 94/33

84 Designated Contracting States :
AT BE CH DE DK ES FR GB IT LI LU NL SE

56 References cited :
EP-A- 0 054 279
EP-A- 0 181 970
EP-A- 0 295 411
PATENT ABSTRACTS OF JAPAN, vol. 9, no. 66
(C-271)[1789], 26th March 1985; & JP-A-59 199
628 (SEKISUI KAGAKU KOGYO K.K.) 12-
11-1984

73 Proprietor : **SEKISUI KAGAKU KOGYO**
KABUSHIKI KAISHA
4-4 Nishitemma 2-chome
Kita-ku
Osaka-shi Osaka 530 (JP)

Proprietor : **SANSHO CO., LTD.**
3-5-4, Hongo
Bunkyo-ku, Tokyo (JP)
Proprietor : **Elsal Co., Ltd.**
6-10, Koishikawa 4-chome
Bunkyo-ku
Tokyo (JP)

72 Inventor : **Azuma, Masato**
3-3-205, Wakayamadal 1-chome,
Shimamotocho
Mishima-gun, Osaka (JP)
Inventor : **Negama, Tsutomu**
8-1, Masago 1-chome
Ibaraki-shi, Osaka (JP)
Inventor : **Yoshida, Mitsuhiko**
900-10, Honjo-shi
Saitama (JP)
Inventor : **Fujimori, Hiroyuki**
1034-1, Ohaza Imai
Honjo-shi, Saitama (JP)

74 Representative : **Hansen, Bernd, Dr.**
Dipl.-Chem. et al
Hoffmann, Elte & Partner
Patent- und Rechtsanwälte,
Postfach 81 04 20
D-81904 München (DE)

EP 0 454 089 B1

Note : Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

Decripti n

The present invention relates to a percutaneously absorbable preparation for the percutaneous administration of eperisone, tolperisone or a salt thereof. Particularly, the present invention relates to a pharmaceutical preparation of eperisone, tolperisone or a salt thereof with excellent percutaneous absorbability.

Eperisone, tolperisone and salts thereof (hereinafter referred to generically as the "invention compound") have been used as remedies for syndromes due to spastic paralysis or paramyotonia due to diseases such as cervicobrachial syndrome, periarthritis of shoulder and lumbago. Generally, the invention compounds are orally administered. When a drug is orally administered, however, the drug absorbed by the intestines is decomposed by the metabolism in the liver at a considerably high ratio before it exhibits a pharmacological effect at an affected part. Since a considerable amount of a drug is absorbed within a short duration in time, an adverse reaction may be liable to occur.

Meanwhile, it has been practiced to make a drug (physiologically active substance) absorbed through the skin in the form of a percutaneously absorbable preparation. The percutaneous administration has various advantages. That is, the drug percutaneously absorbed can reach an affected part without being decomposed by the metabolism in the liver. Further, percutaneous administration hardly causes gastrointestinal disorder which may likely be caused by oral administration. The adverse reaction due to the absorption of a large amount of a drug within a short duration can be reduced by releasing a drug in a rate controlled manner by percutaneous administration. The frequency of administration of a drug can be reduced by keeping the release rate thereof constant for a long period of time.

In the percutaneous administration of a drug, however, it is hard to make absorb the drug in a sufficient amount in many cases since the permeability of the drug through the skin is poor in general. The corneal layer of epidermis acts as a barrier against the invasion of foreign substances into the body, so that a satisfactory amount of a drug to exert its pharmacological action cannot be absorbed through the skin. The percutaneous absorbability is improved by addition of an enhancer for absorbability which can lower the barrier function of the corneal layer.

For example, Japanese Patent Laid-Open No. 52716/1989 discloses a percutaneously absorbable preparation which is improved in the percutaneous absorbability of the invention compound by the addition of a monoglyceride of a fatty acid having 8 to 12 carbon atoms and/or a lactate of a fatty alcohol having 12 to 18 carbon atoms as a percutaneous absorption accelerator. However, the percutaneously ab-

sorbable preparation thus prepared is still insufficient in the percutaneous absorbability of the invention compound. Particularly, a pharmaceutical preparation of sticking type containing such a percutaneous absorption enhancer is still unsatisfactory in the practical use.

EP-A-0 295 411 discloses a pharmaceutical composition for the percutaneous administration which comprises eperisone or tolperisone, or salts thereof as well as a pharmacologically acceptable carrier. Further, the composition contains a monoglyceride of an aliphatic and/or an ester of lactic acid to enhance penetration of the effective ingredients through the skin.

EP-A-0 295 411 and JP-A-59-199 628 disclose polyvinylpyrrolidone copolymers which include significant amounts of comonomers, as an agent for enhancing percutaneous absorption of a drug composition.

According to the invention, an enhancer or accelerator for percutaneous absorption is proposed in combination with the specified pharmacologically active compound.

The present invention aims at solving the above mentioned problems of the prior art and an object thereof is to provide a percutaneously absorbable preparation which permits an effective percutaneous administration of eperisone, tolperisone or a salt thereof.

The present invention relates to a percutaneously absorbable preparation comprising eperisone, tolperisone or a salt thereof, a crosslinked polyvinylpyrrolidone and a base, wherein said crosslinked polyvinylpyrrolidone is water-swellable. The above object can be attained by taking this constitution.

The invention provides a pharmacological composition for percutaneous administration which comprises:

0.05-30% by wt. of eperisone, tolperisone or a salt of either thereof,

0.5-20% by wt. of a water-swellable crosslinked polyvinylpyrrolidone optionally copolymerized with up to, but no more than, 20% by wt. of a polyfunctional comonomer based on the amount of vinylpyrrolidone, and

a base carrier.

It is preferred that the composition further comprises up to 10 percent by weight of a percutaneous absorption enhancer.

It is preferable that the polyvinylpyrrolidone is a copolymer of N-vinyl-2-pyrrolidone and 0.1 to 20 percent by weight, based on the N-vinyl-2-pyrrolidone, of a polyfunctional monomer.

It is preferable that eperisone, a salt thereof, tolperisone and a salt thereof are contained in an amount of not less than their respective saturated solubility and that they are dispersed in the microcrystalline form in the base.

According to a preferable embodiment of the present invention, perisone, tolperisone or a salt thereof is contained in a base in an amount exceeding its solubility and is dispersed therein in a microcrystalline state.

The invention compound used as an active ingredient in the present invention includes eperisone, tolperisone and salts thereof. The salts include chlorides, phosphates and methanesulfonates. The compound may be dissolved in a base which will be described below or mixed therewith in an amount exceeding its solubility and dispersed therein in a microcrystalline state.

The invention compound is contained in the preparation at a proportion of 0.05 to 30% by weight, preferably 0.1 to 20% by weight. When the percutaneously absorbable preparation of the present invention is of sticking type, such as tape, patch or cataplasm, the compound is contained in the medicated layer of the preparation excluding the support at a proportion as described above. The preparation may be used for plaster tape. When the content of the compound is less than 0.05 wt.%, the percutaneous absorption of the drug will be insufficient to give a blood drug concentration enough to exhibit its effect with a practical application area (150 cm² or below). On the contrary, when the content thereof exceeds 30% by weight, the resulting pharmaceutical preparation will be liable to cause base crack. Therefore, for example, when the preparation is of sticking type, the applicability thereof will be poor.

The crosslinked polyvinylpyrrolidone to be used in the present invention is prepared by the copolymerization of N-vinyl-2-pyrrolidone with a polyfunctional monomer and is contained in the pharmaceutical preparation in a particulate state. The polyfunctional monomer to be used in the above copolymerization includes di(meth)acrylates such as hexamethylene glycol di(meth)acrylate, ethylene glycol di(meth)acrylate, triethylene glycol di(meth)acrylate, tetraethylene glycol di(meth)acrylate and polyethylene glycol di(meth)acrylate; tri(meth)acrylates such as trimethylolpropane triacrylate; tetra(meth)acrylates such as tetramethylolmethane tetraacrylate; polyallyl compounds such as diethylene glycol bisallyl carbonate, triallylglycerin and triallyl cyanurate; and polymaleimides such as ethylenebismaleimide. Further, the polyfunctional monomer includes cyclic acid amides such as N,N'-divinylimidazolidone, N,N'-divinylohexahydropyrimidinone and N-vinyl-3-ethylidenepyrrolidone; divinylbenzene; N,N'-methylenebisacrylamide; ethylenebisvinylpyrrolidone; divinyl ketone; butadiene and isoprene. The amount of the polyfunctional comonomer is preferably 0.1 to 20% by weight, still preferably 0.5 to 10% by weight based on the vinylpyrrolidone monomer used. When the amount of the polyfunctional monomer is less than 0.1% by weight, the resulting crosslinked polyvinylpyrrolidone will be

dissolved in a base which will be described below, or will be significantly swollen therewith, so that the retention of the particulate structure thereof in the preparation will be difficult. On the contrary, when the amount exceeds 20% by weight, the resulting crosslinked polyvinylpyrrolidone will be hardly swollen in the pharmaceutical preparation, so that the drug-releasing properties of the preparation will be hardly improved.

Alternatively, the crosslinked polyvinylpyrrolidone can be prepared by treating a soluble non-crosslinked polyvinylpyrrolidone with thionyl chloride, phosphorus trichloride or phosphorus pentachloride in an organic solvent under heating.

The crosslinked polyvinylpyrrolidone may be commercially available one and preferable examples thereof include Kollidon CL^R (a product of BASF) and Polyplasdone XL^R (a product of GAF). The processes for the preparation of these compounds are described in U. S. Patent Nos. 3759880, 3933766, 3689439, 4139688 and 4180633.

The crosslinked polyvinylpyrrolidones described above exhibit proper swellability with water. Accordingly, when a pharmaceutical preparation containing one of the crosslinked polyvinylpyrrolidones is applied to the skin, the preparation is swollen with moisture such as sweat to enhance the drug-releasing properties thereof. The crosslinked polyvinylpyrrolidone is contained in the pharmaceutical preparation of the present invention at a proportion of 0.5 to 20% by weight. When the percutaneously absorbable preparation is of sticking type, the crosslinked polyvinylpyrrolidone is contained in the proportion as described above based on the total weight of the medicated layer. When the proportion of the crosslinked polyvinylpyrrolidone is less than 0.5% by weight, the release of the drug will not be accelerated, while when it exceeds 20% by weight, the tackiness of the preparation will be low particularly when the preparation is in the form of a tape.

The base to be used in the present invention varies depending upon the use of the pharmaceutical preparation. The preparation of the present invention may take a form selected from among tape, patch, cataplasm, ointment and cream. A percutaneous preparation of sticking type such as tape, patch, cataplasm or plaster is prepared by forming a medicated layer on a suitable support. These sticking-type preparations are preferably used in order to control the dose of each application accurately, among which tape and patch are still preferable from the standpoint of the convenience in application.

The base to be used in the tape or patch according to the present invention is one having a tack strength enough to fix the preparation to the surface of the skin at ordinary temperatures for a long time. Examples thereof include acrylic, rubber and silicon pressure-sensitive adhesives, among which acrylic

and rubber pressure-sensitive adhesives are preferably used in respect of tack properties and cost.

The acrylic pressure-sensitive adhesive is preferably a polymer or copolymer comprising one or more monomers selected from among alkyl (meth)acrylates prepared from an aliphatic alcohol having 4 to 18 carbon atoms and (meth)acrylic acid, or a copolymer of an alkyl (meth)acrylate as described above with other functional monomer. Examples of the alkyl (meth)acrylate include butyl acrylate, isobutyl acrylate, hexyl acrylate, octyl acrylate, 2-ethylhexyl acrylate, isooctyl acrylate, decyl acrylate, isodecyl acrylate, lauryl acrylate, stearyl acrylate, butyl methacrylate, isobutyl methacrylate, 2-ethylhexyl methacrylate, isooctyl methacrylate, decyl methacrylate, isodecyl methacrylate, lauryl methacrylate and stearyl methacrylate.

The functional monomers usable in the preparation of the above copolymer are classified into hydroxylated monomers, carboxylated monomers and amide monomers. The hydroxylated monomers include 2-hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate. The carboxylated monomers include α , β -unsaturated carboxylic acids such as acrylic and methacrylic acids; monoalkyl maleates such as butyl maleate; and maleic, fumaric and crotonic acids. Maleic anhydride can also form a copolymer similar to that obtained from maleic acid, thus being usable. The amide monomers include acrylamide; alkyl(meth)acrylamides such as dimethylacrylamide and diethylacrylamide; alkyl ether methylol (meth)acrylamides such as butoxymethylacrylamide and ethoxymethylacrylamide; diacetone acrylamide and vinylpyrrolidone. Further, vinyl acetate, styrene, α -methylstyrene, vinyl chloride, acrylonitrile, ethylene, propylene and butadiene may be also used.

The acrylic pressure-sensitive adhesive can be prepared by copolymerizing monomers as described above according to a conventional process. It is preferable that the alkyl (meth)acrylate be contained in an amount of at least 50% by weight based on the whole comonomers.

The rubber pressure-sensitive adhesive includes natural rubber, synthetic isoprene rubber, polyisobutylene, polyvinyl ether, polyurethane, polyisoprene, polybutadiene, styrene-butadiene copolymers, styrene-isoprene copolymers and styrene-isoprene-styrene block copolymers.

The silicone pressure-sensitive adhesive includes silicone rubbers such as polyorganosiloxane.

If necessary, the above pressure-sensitive adhesive may further contain various additives. Examples of the additives include tackifier such as rosin resin, polyterpen resin, cumarone-inden resin, petroleum resin or terpene-phenol resin; plasticizer such as liquid polybutene, mineral oil, lanolin, liquid isobutylene or liquid polyacrylate; filler and ager resister.

When the percutaneously absorbable prepara-

tion of the present invention is in the form of a cataplasm, the base to be used includes natural polymers such as sodium alginate, gelatin, corn starch and tragacanth gum; cellulose polymers such as methylcellulose, hydroxyethylcellulose and carboxymethylcellulose; starch polymers such as dextrin and carboxymethylstarch; and synthetic polymers such as polyvinyl alcohol, polysodium acrylate, methoxyethylene-maleic anhydride copolymer, polyvinyl ether and polyvinylpyrrolidone. If necessary, the base may contain purified water; a polyhydric alcohol humectant such as glycerin or propylene glycol; an inorganic filler such as kaolin, bentonite, zinc oxide or titanium dioxide; a viscosity modifier; a crosslinking agent and/or an ager resister.

When the pharmaceutical preparation is used as an ointment or a cream, the base includes beeswax, fats and oils, white vaseline, paraffin, Plastibase, 50 w (trade name), higher fatty acids, higher alcohols, emulsifier, macrogols and carboxy vinyl polymers. If necessary, the base may contain a fat-soluble solubilizing agent such as crodamiton, liquid paraffin, isopropyl myristate or diethyl sebacate; purified water; ethanol; a polyhydric alcohol such as glycerol as a water-soluble solubilizing agent and/or a pH regulator.

If necessary, the percutaneously absorbable preparation of the present invention may further contain a suitable absorption accelerator for the purpose of improving the percutaneous absorbability of a drug. Examples of the absorption accelerator include isopropyl myristate, diethyl sebacate, sorbitan monolaurate, glycerol monooleate, sodium oleyl phosphate, sodium lauryl sulfate, octyl phenyl ether, adduct of polyethylene glycol and octyl phenyl ether, lauryl ether, adduct of polyethylene glycol and lauryl ether, sorbitan monooleate, adduct of polyethylene glycol and sorbitan monooleate, lauroyldiethanolamide, lauroylsarcosine, oleoylsarcosine sugar ester, lecithin, glycyrrhetine, urea, salicylic acid, calcium thioglycolate, lactic acid, lactate esters, olive oil, squalene, lanolin, liquid paraffin and glycerin. Particularly, lactates of aliphatic alcohols having 12 to 18 carbon atoms are preferable. Examples thereof include myristyl lactate, lauryl lactate and cetyl lactate.

The absorption accelerator is contained in the pharmaceutical preparation at a proportion of 10% by weight or below, preferably 0.1 to 10% by weight. When the pharmaceutical preparation is of sticking type, the accelerator are contained at a proportion as described above based on the whole medicated layer. When the proportion of the accelerator exceeds 10% by weight, the resulting preparation will be irritant to the skin to cause flare or itch when applied to the skin.

When the percutaneously absorbable preparation of the present invention is in the form of an ointment or a cream, it is prepared by adding the invention compound, a crosslinked polyvinylpyrrolidone and, if

n cessary, absorption accelerator to a base as defined above, followed by mixing.

When the percutaneously absorbable preparation of the present invention is of sticking type, such as tape, patch or cataplasm, it is prepared by forming a medicated layer comprising the invention compound, a crosslinked polyvinylpyrrolidone, a base and, if necessary, absorption accelerator on a suitable support. The process for forming such a layer on a support includes various known application processes such as solution coating, hot-melt coating and electron beam curing emulsion coating, among which solution coating is particularly preferable. According to the solution coating, a sticking-type preparation can be prepared by diluting a base as described above with a proper solvent, adding the invention compound, a crosslinked polyvinylpyrrolidone and, if necessary, an absorption accelerator and various additives to the diluted base to obtain a dispersion, applying the dispersion to the surface of a support and drying the obtained laminate to remove the solvent. It is also prepared by applying the dispersion to a release sheet or liner, drying the formed layer and transferring the layer to a support. The thickness of the medicated layer thus formed on a support is generally from about 30 μm to about 200 μm , though it varies depending upon the objective use. When the thickness is less than 30 μm , the resulting sticking-type preparation will not contain a necessary amount of a drug per unit area. Further, when the preparation is in the form of a tape or a patch, no sufficient tackiness will be attained. On the contrary, when the thickness exceeds 200 μm , the drug present near the support in the medicated layer will difficultly reach the surface of the skin by diffusion, so that the drug contained in the preparation will not be utilized effectively. The medicated layer may be covered with a release sheet in order to protect the layer until service.

The support to be used in the above sticking-type preparation may be any conventional one for sticking-type preparations and examples of the material of the support include cellulose acetate, ethylcellulose, polyethylene terephthalate, plasticized vinyl acetate-vinyl chloride copolymer, nylon, ethylene-vinyl acetate copolymer, plasticized polyvinyl chloride, polyurethane, polyvinylidene chloride and aluminum. These materials may be used either as a single-layer sheet or as a laminate comprising two or more sheets. Alternatively, all of the materials except aluminum may be also used as a woven or nonwoven fabric.

The sticking-type preparation thus prepared is applied to an affected part. When the preparation is a cataplasm, it is fixed to the surface of the skin with an adhesive plaster or the like, since it is poor in tackiness.

The percutaneously absorbable preparation of the present invention is characterized in that the invention compound contained therein can be easily

absorbed into the blood through the skin. The mechanism how this advantageous characteristic is brought about is thought to be as follows, though the details thereof are not apparent. Namely, the crosslinked polyvinylpyrrolidone contained in the pharmaceutical preparation is nonswellable with the invention compound but is swellable with water. Therefore, when the pharmaceutical preparation of the present invention is applied to the surface of the skin, the crosslinked polyvinylpyrrolidone absorbs moisture such as sweat and is swollen therewith to function so as to expel the invention compound from the preparation. By virtue of this function of the crosslinked polyvinylpyrrolidone, the invention compound can be effectively released from the preparation and administered into the blood through the skin.

The percutaneously absorbable preparation of the present invention is characterized in that eperisone, tolperisone or a salt thereof can be effectively absorbed percutaneously.

The preparation of the present invention can be used in various forms such as tape, patch, cataplasm, ointment and cream. Particularly, it is preferably used as a sticking-type preparation such as tape, patch or cataplasm.

Brief Description of the Drawings:

Fig. 1 is a graph showing the percutaneous absorbability of eperisone hydrochloride with respect to the tapes made in the Examples and Comparative Examples.

Fig. 2 is a graph showing the dissolution rate of eperisone hydrochloride with respect to the tapes made in the Examples and Comparative Examples.

Fig. 3 is a graph showing the percutaneous absorbability of tolperisone hydrochloride with respect to the tapes made in the Examples and Comparative Examples.

The present invention will now be described by referring to the following Examples.

Example 1

A copolymer prepared by the copolymerization of 45 parts by weight of 2-ethylhexyl acrylate with 55 parts by weight of 2-ethylhexyl methacrylate was dissolved in ethyl acetate to give a base solution having a solid content of 34% by weight. Four parts by weight of eperisone hydrochloride and 2 parts by weight of Kollidon CL^R (crosslinked polyvinylpyrrolidone, a product of BASF) were added to 100 parts by weight of the base solution and the obtained mixture was thoroughly stirred in a dissolver to give a homogeneous dispersion containing eperisone hydrochloride in a microcrystalline state and Kollidon CL^R in a particulate state. This dispersion was applied to a polyethylene terephthalate release sheet having a thickness

of 45 μm and dried in a Geer oven at 65°C for 25 minutes to form a medicated layer. This layer was transferred to a polyethylene terephthalate film having a thickness of 10 μm to give a tape having a medicated layer containing 10% by weight of eperisone hydrochloride and 5% by weight of Kollidon CL^R and a thickness of 80 μm laminated thereon. In this medicated layer were dispersed Kollidon CL^R in a particulate state and eperisone hydrochloride in a microcrystalline state.

The tape thus made was examined for the percutaneous absorbability and dissolution rate of a drug according to the following methods.

Percutaneous absorbability of drug: The tape made above was cut into a test piece of 60 cm². This test piece was applied to the back of a Japanese white rabbit shorn with an electric clipper or shaver to determine the change in the drug concentration of the plasma with time. The result is given in Fig. 1 together with those of Examples 2 and 3 and Comparative Examples 1 to 3 which will be described below.

Dissolution rate of drug: The tape was examined for dissolution rate of a drug with equipment as defined in the Dissolution Test Method 2 (paddle method) of The Pharmacopoeia of Japan (eleventh edition). First, the tape was cut into a test piece of 10 cm². The support side of this test piece was fixed to a stainless steel fixing device with a double-coated tape and the release sheet was removed from the medicated layer. The fixing device thus treated was sunk at the bottom of a measuring vessel containing 200 ml of distilled water with the medicated layer of the tape facing upward. The resulting system was allowed to stand for a predetermined period of time while keeping the temperature of the distilled water at 37°C and the rotational speed of the paddle at 100 rpm. Thereafter, the amount of the drug dissolved in the distilled water was measured to determine the change in the amount of the drug dissolved therein with time. The result is given in Fig. 2 together with those of Examples 2 and 3 and Comparative Examples 1 to 3.

Example 2

100 parts by weight of a styrene-isoprene-styrene block copolymer (a product of Shell, Kraton D1107), 15 parts by weight of polybutene (a product of Nippon Oil Co., Ltd., HV-300), 160 parts by weight of a saturated alicyclic hydrocarbon resin (a product of Arakawa Chemical Industry Co., Ltd., Alcon P-90) and 3 parts by weight of butylhydroxytoluene were added to cyclohexane, followed by mixing. Thus, a base solution having a solid content of 42.5% was obtained. 5 parts by weight of eperisone hydrochloride and 2.5 parts by weight of Polyplasdon XL-10^R (a product of GAF) were added to 100 parts by weight of the base solution. The obtained mixture was thoroughly stirred in a dissolver to give a homogeneous

dispersion containing eperisone hydrochloride in a microcrystalline state and Polyplasdon XL-10^R in a particulate state. A tape was made from this dispersion in a similar manner to that of Example 1. The obtained tape was a laminate comprising a polyethylene terephthalate film having a thickness of 10 μm and a medicated layer having a thickness of 80 μm . This layer contained 10% by weight of eperisone hydrochloride and 5% by weight of Polyplasdone XL-10^R. The Polyplasdone XL-10^R was dispersed in the medicated layer in a particulate state and the eperisone hydrochloride was dispersed therein in a microcrystalline state.

Example 3

A copolymer prepared by the copolymerization of 85 parts by weight of 2-ethylhexyl acrylate with 15 parts by weight of vinylpyrrolidone was dissolved in ethyl acetate to give a base solution having a solid content of 33.2% by weight. 4 parts by weight of eperisone hydrochloride, 2 parts by weight of Kollidon CL^R and 0.8 part by weight of cetyl lactate were added to 100 parts by weight of the base solution. The obtained mixture was thoroughly stirred in a dissolver to give a homogeneous dispersion in which microcrystalline eperisone hydrochloride and particulate Kollidon CL^R were homogeneously dispersed. A tape was made from this dispersion in a similar manner to that of Example 1. The medicated layer of the obtained tape contained 10% by weight of eperisone hydrochloride, 5% by weight of Kollidon CL^R and 2% by weight of cetyl lactate. The Kollidon CL^R was dispersed in a particulate state in the layer and the eperisone hydrochloride was dispersed in a microcrystalline state therein.

Comparative Example 1

A tape was made by the same procedure as that of Example 1 except that no Kollidon CL^R was added. The eperisone hydrochloride content of the medicated layer of the tape was 10.5% by weight. The eperisone hydrochloride was dispersed in the layer in a microcrystalline state.

Comparative Example 2

A tape was made by the same procedure as that of Example 2 except that no Polyplasdone XL-10^R was added. The eperisone hydrochloride content of the medicated layer of the tape was 10.5% by weight. The eperisone hydrochloride was dispersed in the layer in a microcrystalline state.

Comparative Example 3

A tape was made by the same procedure as that

of Example 3 except that no Kollidon CL^R was added. The medicated layer of the obtained tape contained 10.5% by weight of eperisone hydrochloride and 2.1% by weight of cetyl lactate. The eperisone hydrochloride was dispersed in the layer in a microcrystalline state.

Example 4

A tape was made in a similar manner to that of Example 1 except that tolperisone hydrochloride was used instead of the eperisone hydrochloride. The medicated layer of the obtained tape contained 10% by weight of tolperisone hydrochloride and 5% by weight of Kollidon CL^R. The Kollidon CL^R was dispersed in the layer in a particulate state and the tolperisone hydrochloride was dispersed therein in a microcrystalline state. The obtained tape was examined for the percutaneous absorbability of a drug in a similar manner to that of Example 1. The result is given in Fig. 3 together with those of Examples 5 and 6 and Comparative Examples 4 to 6 which will be described below.

Example 5

A tape was made in a similar manner to that of Example 2 except that tolperisone hydrochloride was used instead of the eperisone hydrochloride. The medicated layer of the obtained tape contained 10% by weight of tolperisone hydrochloride and 5% by weight of Polyplasdone XL-10^R. The Polyplasdone XL-10^R was dispersed in the layer in a particulate state and the tolperisone hydrochloride was dispersed therein in a microcrystalline state.

Example 6

A tape was made in a similar manner to that of Example 3 except that tolperisone hydrochloride was used instead of the eperisone hydrochloride. The medicated layer of the tape contained 10% by weight of tolperisone hydrochloride, 5% by weight of Kollidon CL^R and 2% by weight of cetyl lactate. The Kollidon CL^R was dispersed in the layer in a particulate state and the tolperisone hydrochloride was dispersed therein in a microcrystalline state.

Comparative Example 4

A tape was made in a similar manner to that of Example 4 except that no Kollidon CL^R was added. The tolperisone hydrochloride content of the medicated layer of the obtained tape was 10.5% by weight and the eperisone hydrochloride was dispersed in the layer in a microcrystalline state.

Comparative Example 5

A tape was made in a similar manner to that of Example 5 except that no Polyplasdone XL-10^R was added. The tolperisone hydrochloride content of the medicated layer of the obtained tape was 10.5% by weight and the tolperisone hydrochloride was dispersed in the layer in a microcrystalline state.

Comparative Example 6

A tape was made in a similar manner to that of Example 6 except that no Kollidon CL^R was added. The medicated layer of the obtained tape contained 10.5% by weight of tolperisone hydrochloride and 2.1% by weight of cetyl lactate. The tolperisone hydrochloride was dispersed in the layer in a microcrystalline state.

Example 7

65 parts by weight of white vaseline was heated to 70°C, followed by the addition thereto of 20 parts by weight of purified lanolin, 5 parts by weight of Kollidon CL^R and 10% by weight of eperisone hydrochloride. The obtained mixture was kneaded and cooled to give an ointment according to the present invention.

Example 8

10 parts by weight of eperisone hydrochloride was added to 5 parts by weight of propylene glycol heated to 60°C to give a mixture wherein part of the eperisone hydrochloride was dissolved in the propylene glycol. A mixture previously prepared by mixing 5 parts by weight of Kollidon CL^R and 3 parts by weight of cetyl lactate with 77 parts by weight of Plastibase (registered trademark of Squibb Japan Inc.; comprising 95 parts by weight of liquid paraffin and 5 parts by weight of polyethylene having a molecular weight of 10000 to 30000) under heating at 60°C was added to the above mixture. The resulting mixture was cooled to room temperature under stirring to give an ointment according to the present invention.

Example 9

65 parts by weight of white vaseline was heated to 70°C, followed by the addition thereto of 20 parts by weight of purified lanolin, 5 parts by weight of Kollidon CL^R and 10 parts by weight of tolperisone hydrochloride. The obtained mixture was kneaded and cooled to give an ointment according to the present invention.

Example 10

5 parts by weight of propylene glycol was heated to 60°C, followed by the addition thereto of 10 parts

by weight of tolperisone hydrochloride. Thus, a mixture wherein part of the tolperisone hydrochloride was dissolved in the propylene glycol was obtained. A mixture previously prepared by mixing 5 parts by weight of Kollidon CL^R and 3 parts by weight of cetyl lactate with 77 parts by weight of Plastibase under heating at 60°C was added to the above mixture. The obtained mixture was cooled to room temperature under stirring to give an ointment according to the present invention.

As shown in Figs. 1 and 2, the tapes of Examples 1 to 3 according to the present invention are excellent in the percutaneous absorbability of eperisone hydrochloride and the dissolution rate thereof. On the other hand, the tapes of Comparative Examples 1 to 3 containing no crosslinked polyvinylpyrrolidone are poor in the percutaneous absorbability and dissolution rate.

As shown in Fig. 3, the tapes of Examples 4 to 6 according to the present invention are superior to those of Comparative Examples 4 to 6 containing no crosslinked polyvinylpyrrolidone in the percutaneous absorbability of tolperisone hydrochloride and the dissolution rate thereof.

Claims

**Claims for the following Contracting States :
AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

1. A pharmacological composition for percutaneous administration which comprises:
0.05-30% by wt. of eperisone, tolperisone or a salt of either thereof,
0.5-20% by wt. of a water-swelling cross-linked polyvinylpyrrolidone optionally copolymerized with up to, but no more than, 20% by wt. of a polyfunctional comonomer based on the amount of vinylpyrrolidone, and
a base carrier.
2. A composition according to Claim 1, wherein said polyvinylpyrrolidone is a polymer of N-vinyl-2-pyrrolidone.
3. A composition according to Claim 1, which further comprises up to 10% by wt. of an additional percutaneous absorption enhancer.
4. A composition according to Claim 1, wherein eperisone, tolperisone or a salt of either thereof is contained in an amount of not less than its respective saturated solubility and it is dispersed in the form of microcrystals in the base.

Claims for the following Contracting State : ES

1. A process for preparing a pharmacological composition for percutaneous administration which comprises the step of mixing a base carrier, 0.05-30% by wt. of eperisone, tolperisone or a salt of either thereof, and 0.5-20% by wt. of a water-swelling crosslinked polyvinylpyrrolidone optionally copolymerized with up to, but no more than, 20% by wt. of a polyfunctional comonomer based on the amount of vinylpyrrolidone.
2. A process according to Claim 1, wherein said polyvinylpyrrolidone is a polymer of N-vinyl-2-pyrrolidone.
3. A process according to Claim 1, wherein the composition further comprises up to 10% by wt. of an additional percutaneous absorption enhancer.
4. A process according to Claim 1, wherein eperisone, tolperisone or a salt of either thereof is contained in an amount of not less than its respective saturated solubility and it is dispersed in the form of microcrystals in the base.

Patentansprüche

Patentansprüche für folgende

**Vertragsstaaten : AT, BE, CH, DE, DK, FR,
GB, IT, LI, LU, NL, SE**

1. Eine pharmakologische Zusammensetzung für die perkutane Verabreichung, welche:
0,05-30 Gewichts-% Eperison, Tolperison oder eines Salzes eines von diesen,
0,5-20 Gewichts-% eines mit Wasser quellbaren, vernetzten Polyvinylpyrrolidons, welches gegebenenfalls mit- bezogen auf die Menge des Vinylpyrrolidons - bis zu aber nicht mehr als 20 Gewichts-% eines polyfunktionalen Comonomers copolymerisiert ist und
einen Basisträger beinhaltet.
2. Eine Zusammensetzung gemäß Anspruch 1, worin das genannte Polyvinylpyrrolidon ein Polymer von N-Vinyl-2-pyrrolidon ist.
3. Eine Zusammensetzung gemäß Anspruch 1, welche ferner bis zu 10 Gewichts-% eines zusätzlichen Verstärkers der perkutanen Absorption einschließt.
4. Eine Zusammensetzung gemäß Anspruch 1, worin Eperison, Tolperison oder ein Salz eines von diesen in einer Menge von nicht weniger als

der entsprechenden Sättigungslöslichkeit enthält und in der Form von Mikrokristallen in der Basis dispergiert ist.

Patentansprüche für folgenden

Vertragsstaat : ES

1. Ein Verfahren zur Herstellung einer pharmakologischen Zusammensetzung für die perkutane Verabreichung, welches den Schritt des Vermischens eines Basisträgers, von 0,05 bis 30 Gewichts-% Eperison, Tolperison oder eines Salzes eines von diesen und von 0,5 bis 20 Gewichts-% eines in Wasser quellbaren, vernetzten Polyvinylpyrrolidons einschließt, welches gegebenenfalls mit - bezogen auf die Menge des Vinylpyrrolidons - bis zu aber nicht mehr als 20 Gewichts-% eines polyfunktionalen Comonomers copolymerisiert ist.
2. Ein Verfahren nach Anspruch 1, wobei das genannte Polyvinylpyrrolidon ein Polymer von N-Vinyl-2-pyrrolidon ist.
3. Ein Verfahren nach Anspruch 1, wobei die Zusammensetzung weiter bis zu 10 Gewichts-% eines zusätzlichen Verstärkers der perkutanen Absorption einschließt.
4. Ein Verfahren gemäß Anspruch 1, wobei Eperison, Tolperison oder ein Salz eines von diesen in einer Menge von nicht weniger als der entsprechenden Sättigungslöslichkeit enthalten und in der Form von Mikrokristallen in der Basis dispergiert ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique pour administration percutanée qui comprend :
0,05-30% en masse d'épérison, de tolperison ou d'un sel de l'une des deux,
0,5-20% en masse d'une polyvinylpyrrolidone réticulée gonflable avec l'eau éventuellement copolymérisée avec jusqu'à, mais pas plus de, 20% en masse d'un comonomère polyfonctionnel en se basant sur la quantité de vinylpyrrolidone, et
un véhicule base.
2. Composition selon la revendication 1, dans laquelle ladite polyvinylpyrrolidone est un polymère de N-vinyl-2-pyrrolidon.

3. Composition selon la revendication 1, qui comprend de plus jusqu'à 10% en masse d'un agent supplémentaire augmentant l'absorption percutanée.

4. Composition selon la revendication 1, dans laquelle l'épérison, la tolperison ou un sel de l'une des deux est contenu dans une proportion non inférieure à sa solubilité respective saturée et est dispersé dans la base sous forme de microcristaux.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'une composition pharmaceutique pour administration percutanée qui comprend l'étape de mélange d'un véhicule base, 0,05-30% en masse d'épérison, de tolperison ou d'un sel de l'une des deux, et 0,5-20% en masse d'une polyvinylpyrrolidone réticulée gonflable avec l'eau éventuellement copolymérisée avec jusqu'à, mais pas plus de 20% en masse d'un comonomère polyfonctionnel en se basant sur la quantité de vinylpyrrolidone.
2. Procédé selon la revendication 1, dans lequel ladite polyvinylpyrrolidone est un polymère de N-vinyl-2-pyrrolidone.
3. Procédé selon la revendication 1, dans lequel la composition comprend de plus jusqu'à 10% en masse d'un agent supplémentaire augmentant l'absorption percutanée.
4. Procédé selon la revendication 1, dans lequel l'épérison, la tolperison ou un sel de l'une des deux est contenu dans une proportion non inférieure à sa solubilité respective saturée et est dispersé dans la base sous forme de microcristaux.

Fig.1

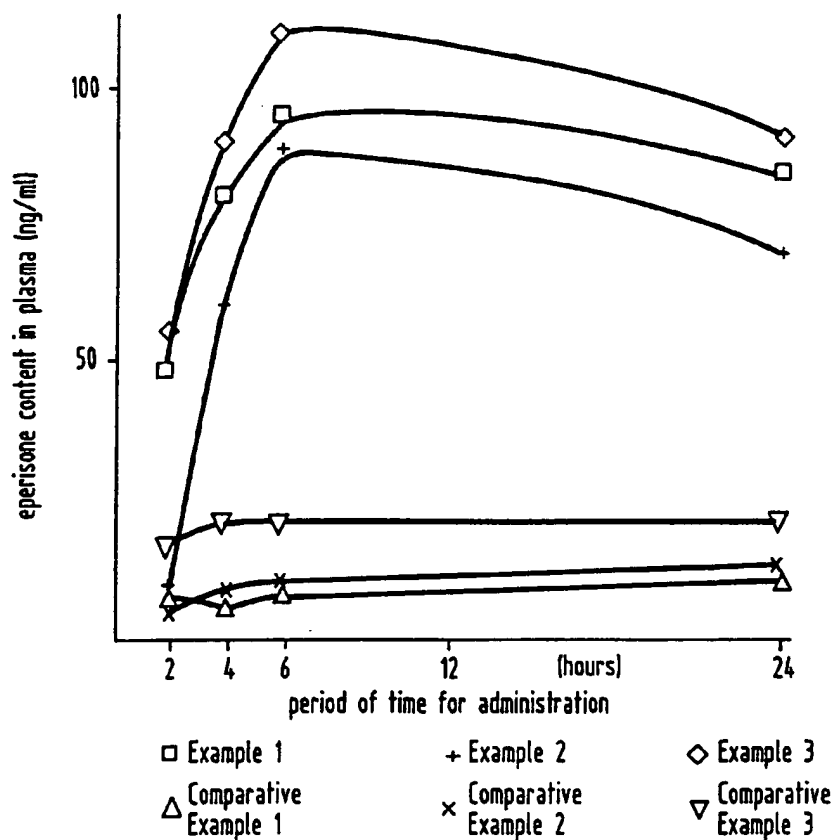


Fig.2

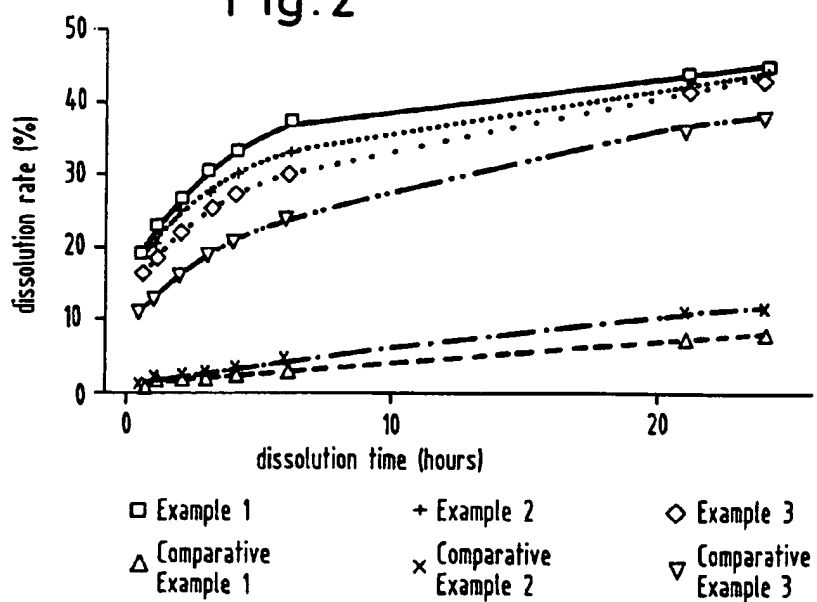


Fig. 3

